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Therapeutic Apheresis in Glomerular Diseases after Kidney Transplantation

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Abstract

Therapeutic apheresis is an extracorporeal treatment that selectively separates abnormal cells or substances from the blood that are linked with or cause certain disease states. It is widely used in transplantation medicine as an adjunctive therapeutic option.

In kidney transplantation (KT), recurrent and de novo glomerular diseases represent the third most common cause of graft failure beyond the first year after transplantation, as current therapeutic options are limited. Evidence to support the use of therapeutic apheresis in these conditions is scarce, as it is only supported by observational studies. The purpose of this review was to examine and clarify the potential role of therapeutic apheresis and describe current evidence in the treatment of recurrent and de novo glomerular diseases after KT.

Keywords: glomerular diseases; kidney transplantation; therapeutic apheresis

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Introduction

Recurrent and de novo glomerular diseases after kidney transplantation (KT) have a powerful impact on transplant survival. After death with a functioning graft and chronic rejection represent the third most common cause of graft failure beyond the first year from KT (1). The Renal Allograft Disease Registry (RADR) data, a consortium of six American transplant centers, examining the rate of recurrent and de novo glomerular diseases after KT, showed a prevalence of 2.8% after 2 years, 9.8% after 5 years, and 18.5% after 8 years of follow-up. In addition, the occurrence of graft failure in recipients with recurrent or de novo glomerular disease was double that of those who did not experience these clinical conditions after KT (2). Briganti *et al.*, in analyzing registry data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), found that 0.5% of grafts within 1 year after KT, 3.7% within 5 years, and 8.4% within 10 years were lost due to recurrent glomerular disease (1). However, the incidence and outcomes of recurrence vary to a great extent. For example, primary focal segmental glomerulosclerosis (FSGS) and C3 glomerulopathy recur frequently; however, the disease tends to have a slow progression in terms of graft loss, and graft survival beyond 10 years is typical (1). On the other hand, anti-glomerular basement membrane (GBM) disease and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis recur

only rarely, but when it does, it is likely to cause rapid graft loss. In the case of complement-mediated atypical hemolytic uremic syndrome (aHUS), recurrence and its impact on graft survival are dependent on the complement pathway mutation responsible.

The treatment of these conditions is often challenging for transplant nephrologists. Therapeutic apheresis (TA) techniques are widely used in KT in desensitization protocols for ABO-incompatible KT, in patients with preformed HLA-antibodies and those undergoing treatment for antibody-mediated rejection (AMR). Although evidence from adequately powered randomized controlled trials supporting the use of TA to treat recurrent and de novo glomerular diseases after KT is lacking, because of the rarity of these diseases, the use of TA, mainly therapeutic plasma exchange (TPE), is widespread in transplant centers. This review examines the evidence supporting the application of TA in treating recurrent and de novo glomerular diseases after KT.

Recurrence of primary focal segmental glomerulosclerosis

Around 30% of the patients with primary FSGS experience disease recurrence after first KT, and in one series, early graft loss occurred at an average of 24 months after diagnosis of recurrence in 14 among 25 patients with recurrent FSGS (3). The possibility of the disease to recur is even higher than 75% after a second KT when the first graft failed because of recurrence (4).

Primary FSGS is probably triggered by a circulating permeability factor that targets the glomerular filtration barrier, especially podocytes. Until now, different plasma molecules have been hypothesized to be implicated in the disease pathogenesis. However, none of them have demonstrated a clear pathogenic correlation (5). Delville *et al*. (6) have recently described a panel of seven antibodies (CD40, PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2) that predict FSGS recurrence after KT, with 92% accuracy. An elevation of the titers of anti-CD40 antibody alone, in the period before transplantation, had the best prediction (78% accuracy), with the disease recurrence after KT (6). Furthermore, the administration of anti-CD40 antibodies, purified from patients with FSGS recurrence, in cultures of human podocytes has been proven to be particularly pathogenic (6).

Over the years, for removing the putative circulating permeability factor responsible for the pathogenesis of the disease, TPE and Immuno-Absorption (IA) (with either a staphylococcal protein A [SPA] or anti-IgG column), alone or in sequence with cyclophosphamide, have been employed with benefit in patients with recurrent disease after KT (7–11). In support of this hypothesis, Dantal *et al*. (11) showed that the administration to rats of material eluted from SPA columns coming from patients with recurrent FSGS after KT result in a substantial increase in albuminuria.

In a systematic review of the literature, Ponticelli highlighted that about 70% of children and 63% of adult transplant recipients with FSGS recurrence who have been treated with TPE or IA sessions had complete or partial remission of proteinuria (12). Two recent meta-analyses have published comparable outcomes (13,14).

There are currently no precise indications on the duration and frequency of TPE sessions. A therapeutic regimen of TPE sessions typically used consists of 1.5 plasma volume exchanges for three consecutive days following treatment on alternate days for a total duration of 2 weeks (15).

TPE sessions have also been applied in protocols with various immunosuppressive agents. In a series of 10 patients, Canaud *et al*. (16) showed favorable outcomes by combining frequent TPE sessions, slowly tapered down for 9 months, with intravenous cyclosporine plus high-dose steroids and mycophenolate.

The use of Rituximab (RTX) in the recurrence of FSGS after KT has rapidly increased with beneficial outcomes in the last 10 years (17,18). RTX, other than being a selective depleting agent of B lymphocytes, provides a direct protective effect on podocytes. Fornoni *et al*. showed that RTX protects sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) and acid sphingomyelinase (ASMase) by binding to SMPDL-3b, a protein that is mainly expressed in the lipid rafts of podocytes, and could be a target of the permeability factor (19,20). As evidenced in several case reports, the use of RTX combined with TPE looks to be more effective than the sole use of TPE (21,22). Of importance, the mean percentage of RTX removal during a first TPE session range between 47 and 54% when TPE is performed between 24 and 72 h after RTX infusion (23). This pharmacokinetic observation should be taken into account for RTX re-dosing after TPE sessions.

Recently, Martin-Moreno *et al*. (24) presented the case of a male patient with severe recurrence of FSGS (massive proteinuria) after KT without response to TPE sessions, and partial remission to a combination of IA and cycles of RTX. The importance of IA, as an alternative to TPE, in the treatment of recurrent FSGS after KT, and in general in the case of idiopathic nephrotic syndrome, has been highlighted in a recent review by Kronbichler *et al*. (25). Now randomized trials are needed to draw conclusions on whether IA is superior to TPE in terms of efficacy, safety, and quality of life.

Complement-mediated atypical hemolytic uremic syndrome

Complement-mediated aHUS is a rare disease that mainly occurs due to gene mutations of complement factors. There have been identified loss-of-function mutations in regulatory

proteins of the alternative pathway of the complement system (factor H, factor I, and membrane cofactor protein [MCP]) or gain-of-function mutations in activators (C3 and factor B) (26). Furthermore, complement-mediated aHUS may be the result of autoimmune processes, through the production of auto-antibodies against complement regulatory proteins (26).

Mutations affecting the protein factors H, I, B, and C3 are associated with a high risk of recurrence (75%), and an even higher risk of graft failure in the first posttransplant year (over 90%), as these are circulating proteins that persist in recipients (27). In contrast, mutations that affect MCP are associated with a low degree of recurrence (approximately 20%) and better survival of the graft since the transplanted kidney expresses the normal protein (28).

TPE is capable of removing auto-antibodies against complement proteins and mutant circulating complement regulatory proteins, replacing them with no defective components; but, its use in the prevention of recurrence, before transplantation, and in the case of recurrence of complement-mediated aHUS posttransplantation has shown poor therapeutic results (29).

The introduction of eculizumab, an anti-C5 monoclonal antibody, positively changed the outcomes and questioned the role of TPE in the treatment of aHUS. The alleged clinical benefits of TPE in prophylactic protocols before transplantation, in addition to eculizumab used by some transplant centers (30), remain unclear and controversial. TPE remains a therapeutic alternative if eculizumab is not available for patients with autoantibodies against factor H and in the case of persistent thrombocytopenia after the initial days of administration of eculizumab (31,32). Attention should be made in case of a TPE session after eculizumab infusion because of increased drug clearance TPE induced. Therefore, an extra dose of eculizumab within 60 min after a TPE is recommended (33).

De novo thrombotic microangiopathy

The occurrence of de novo thrombotic microangiopathy (TMA) posttransplantation could be the result of pathogenetic processes that induce TMA in the general population. However, the most common causes that induce TMA after KT are: i) drug-induced TMA due to calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, ii) ischemia-reperfusion injury, iii) AMR, and iv) viral infections (34).

If clinical improvement does not occur after changing the immunosuppressive regimen, in the case of drug-induced TMA, or after treating the underlying infection, TPE may find application in an attempt to stop further damage to the graft even if the levels of evidence are low for such use (35). If eculizumab is available, it becomes the treatment of choice in these cases (36,37).

When TMA is associated with AMR, the combined use of TPE and intravenous immunoglobulin (IVIG) confer favorable outcomes for the survival of the graft (38). Eculizumab becomes the preferred treatment in AMR-associated TMA if hemolysis persists in spite of the use of TPE, and in the TPE-dependent patients (34).

Recurrence of C3 glomerulopathies

C3 glomerulopathies (C3G) are rare forms of glomerulonephritis that include dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), distinguished by structural characteristics observed on electron microscopy (39). Both subtypes are caused by excessive activation of the alternative complement pathway, which results either from C3 convertase-stabilizing autoantibodies, called C3 nephritic factors (C3NeFs), and other antibodies directed against factor B and factor H or from mutations of factor I, MCP, C3, factor B, factor H, and mutations of the complement factor H related proteins (CFHRs) gene cluster (40).

The recurrence rate of DDD after KT is approximately 80–100%, while the reported recurrence rate of C3GN is greater than 50% (41,42). Factors associated with an increased risk of recurrence include persistently low C3 levels and living-donor KT (43). Recurrent C3G is typically manifested within 1–2 years following KT and often results in graft loss (50% of patients) (41,42). Recurrence occurs earlier and is more aggressive if associated with monoclonal gammopathy (42).

Currently, there are no controlled studies on which to base therapeutic recommendations for recurrent C3G. We suggest that patients should be switched to mycophenolate mofetil (MMF) therapy, if it is not already part of their maintenance immunosuppression regimen.

TPE represents a therapy of unclear benefit. TPE has been proved to prevent disease progression in some patients with DDD in native kidneys with circulating C3NeFs, probably by removal of the pathologic autoantibodies (44). However, McCaughan *et al.* (45) reported that TPE was ineffective in a patient with recurrent DDD after KT, in spite of effective removal of C3NeF. Recently, Kumar *et al.* (46) demonstrated response to TPE in three of four patients with early recurrent C3G (median time for posttransplant recurrence was 3 days) and circulating autoantibodies to complement pathway regulators (two cases had positive C3NeF and one had anti-complement factor-H autoantibodies). All patients underwent five sessions of alternate-day TPE (40 ml/kg/session with membrane filter) using fresh-frozen plasma (FFP) and albumin as the replacement fluid (46). If TPE is used in such patients, we suggest alternate-day TPE, at least initially. Then, TPE should be maintained until C3NeF levels decrease by at least 50%, provided that there is simultaneous stabilization of graft function.

Among patients who have a known serum factor deficiency, as an example, a genetic cause of factor H deficiency, we suggest to begin intermittent FFP infusions or TPE before KT and extend this treatment after transplantation while monitoring for clinical evidence of disease recurrence. If such patients remain free of recurrence, the FFP infusions or TPE may be tapered off with continued monitoring for signs of recurrence.

Eculizumab is an alternative to TPE, which has been used with variable success in patients with recurrent C3G (47,48). Avacopan, an orally administered selective C5a receptor inhibitor, which was recently found to be effective in the treatment of ANCA-associated vasculitis (49), is now tested in a randomized, double-blind, placebo-controlled, phase 2 study (ClinicalTrials.gov Identifier: NCT03301467), in biopsy-proven C3G, either DDD or C3GN, with or without a renal transplant.

Antiphospholipid antibody syndrome and lupus nephritis

Antiphospholipid antibody syndrome is a multisystem autoimmune disease clinically manifested by multiple thrombotic episodes in both venous and arterial circulation, and serologically characterized by the presence of antiphospholipid (aPL) antibodies. APS can represent a primary nosological entity or be secondary to other autoimmune diseases, mainly systemic lupus erythematosus (SLE) (50).

The kidney can be damaged by the occlusion of the glomerular capillaries up to that of the main artery and vein (50). Graft loss due to a thrombotic event of graft vein, graft artery, or even a TMA in the early postoperative period represents the most frequent causes of KT failure in patients with *Antiphospholipid syndrome* (APS) (51). In addition, several studies have highlighted the fact that hemodialysis patients, and consequently the recipients of KT, have a high prevalence of circulating aPL, potentially harmful to the graft (52,53).

Treatment of KT recipients affected by APS with long-term warfarin, for the prevention of thrombotic events, is strongly recommended. In addition, many transplant centers prefer to treat, in the peritransplant period, all patients with aPL positivity and history of thrombotic events (54,55). However, the treatment of these patients with oral anticoagulants increases the risk of bleeding, which could result in an early loss of graft in the immediate posttransplant period. Furthermore, it must be considered that thrombotic events can occur in 40% of cases even during anticoagulant therapy (56).

Prophylactic treatment with TPE for the removal of circulating APL, in addition to maximal oral anticoagulant therapy, before a living-donor KT has proven effective in a patient with primary APS (57) and in the case of a recipient with secondary APS due to SLE (58). However, in cases of catastrophic APS (CAPS), which occur with diffuse TMA (vascular occlusion affecting three or more organ systems) (59), prophylactic treatment with eculizumab to prevent recurrence after KT must be considered as the most suitable treatment after being successfully used in a KT recipient together with systemic anticoagulation and standard immunosuppression (60).

Barbour *et al*. (51) reported a case of acute recurrence of TMA in a recipient of KT affected by APS and lupus nephritis, which has been effectively treated with TPE even with the presence of moderate irreversible damage to the functionality of the graft. These data suggest that further studies are required.

Recurrent and de novo anti-glomerular basement membrane antibody disease

Anti-GBM antibody disease histologically recurs to the graft in up to 50% of cases if circulating anti-GBM antibodies persist at the time of transplantation (61,62). However, clinically manifested cases of recurrent anti-GBM antibody disease are limited, as most patients are asymptomatic (61). Different cohorts described that de novo anti-GBM antibody disease can occur in 0.5–10% of KT recipients with Alport syndrome, developing anti-GBM antibodies to a collagen component expressed by the graft [alpha5 (IV) NC1] that is missing in patients with Alport (63–65). The explanation for the differences in the incidence may relate to different transplant immunosuppression protocols or different thresholds for diagnosis and coding of posttransplant anti-GBM antibody disease used in the various series.

The therapeutic approach is the same as that used in non-transplanted patients. TA must be used promptly for the removal of the harmful autoantibodies, in addition to corticosteroids plus cyclophosphamide or RTX, which are useful to inhibit further antibody production (62). AI and TPE have similar results (66,67).

The endopeptidase IdeS (Immunoglobulin G degrading enzyme of Streptococcus pyogenes), an enzyme that is capable of cleaving both circulating and membrane-bound human IgG subclasses into $F(ab')_2$ and Fc fragments, is a promising new therapeutic approach in the treatment of anti-GBM antibody disease. Soveri *et al*. (68) showed rapid clearance of anti-GBM antibodies (within minutes) in three no transplant patients with severe, and refractory to standard treatment, anti-GBM nephritis. Rebound of anti-GBM antibodies occurred in all three cases, even if it was mild in patients 1 and 3, and easily managed with TPE. Clinical trials are necessary to determine the clinical utility of this new treatment option. GOOD-IDES is an open-label ongoing phase II study to evaluate the efficacy and safety of IdeS in anti-GBM antibody disease (ClinicalTrials.gov identifier: NCT03157037).

Recurrence of antineutrophil cytoplasmic antibody-associated vasculitis

Recurrence of ANCA-associated vasculitis in KT recipients is rare. In a recent review of 11 studies that included a total of 441 KT recipients, the prevalence of recurrent ANCA-associated vasculitis was 10% (69). In case of relapse, the therapeutic options are the same as in non-transplanted patients. Both cyclophosphamide and RTX have shown their efficacy in the event of a posttransplant recurrence (70).

TPE is recommended in addition to corticosteroids and either cyclophosphamide or RTX in cases where recurrence occurs with alveolar hemorrhage, severe segmental necrotizing glomerulonephritis with serum creatinine above 4.0 mg/dL, and concurrent anti-GBM disease (70–72). However, Walsh *et al*. (73), in the recently published results of the Plasma Exchange and Glucocorticoids for Treatment of ANCA-associated vasculitis (PEXIVAS) trial, did not show that the addition of plasma exchange (PLEX) to standard therapy conferred benefits in nontransplant patients with severe ANCA-associated vasculitis in terms of lower incidence of death or End-Stage Kidney Disease (ESKD). In the interim of no data in transplant patients, we recommend that PLEX be considered in any patient who is not responsive to conventional therapy.

The most promising advancement for remission induction therapy in severe organ- or life-threatening ANCA-associated vasculitis is avacopan. Recently, the CLEAR study, a phase 2, randomized, double-blind, placebo-controlled trial, met its primary endpoint, indicating that avacopan can replace high-dose corticosteroids efficiently and safely in patients with newly diagnosed or relapsing ANCA-associated vasculitis (49). The results of the ADVOCATE study, a phase 3 trial, will assess the safety and effectiveness of avacopan as an alternative to prednisone in inducing and maintaining remission in patients with ANCA-associated vasculitis; topline results are anticipated to be published by Q3 2020 (74).

Conclusion

The application of TA is currently used in several glomerular diseases after KT. However, strong evidence is scarce as the rarity of these conditions implies that a high standard of quality randomized clinical trials (RCTs) are missing. In addition, in the era of new and emerging biological immunosuppressive therapies with an increasing number of specific actions and immune targets directed against cell-surface antigens or plasma-soluble molecules, the use of TA as an adjunctive therapeutic option becomes even more challenging in the study of future therapeutic protocols, which will best address open issues for better clinical outcomes. Growing international collaboration is demanded to improve the quality of future studies in this area.

Conflicts of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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